REMARKS / ARGUMENTS

Support for Amendments

The amendments are supported throughout the specification and drawings as originally filed. The following provides specific reference to passages in support of each amendment.

Claim 1 is newly amended to recite the biocompatible porous membrane having porosity sufficient to allow cells to migrate therethrough from the upper chamber to the lower chamber. Claim 1 is also amended to recite the porous membrane permits attachment of cells that have migrated to the lower chamber on one or more of at least two electrodes of the lower chamber.

Support for each may be found in paragraph [0016], which provides in part,

> "The device includes an upper chamber adapted to receive and retain a cell sample, a lower chamber having at least two electrodes, and a biocompatible porous membrane having a porosity sufficient to allow cells to migrate therethrough. The membrane is disposed in the device so as to separate the upper and lower chambers from one another. Migration of cells through the porous membrane permits contact between the migrating cells and one or more electrodes of the lower chamber. "

Claim 1 is also amended to recite the at least two electrodes are partially exposed through pores of the porous membrane. Support may be found in paragraph [00121], which provides in part,

> "If the fabrication process for fabricating the holes and electrodes or electrode structures on the biocompatible membranes permits, it may be possible to ensure the pores for cell migration/invasion are located at regions corresponding to the electrode surfaces, rather than in the gaps between electrodes or electrode elements...The advantage of having the pores for cell migration/invasion located on the regions of the membrane which correspond to the electrode areas is that when cells migrate through a pore, they come into contact with and attach to the electrode surface as they exit the pores in the membrane."

Claim 11 has been rewritten in independent form and thus to recite all limitations in previous claim 1.

Claim 24 is amended to recite wherein the two or more electrodes are partially exposed through pores of the porous membrane. Support may be found in paragraph [00121], which provides in part,

> "If the fabrication process for fabricating the holes and electrodes or electrode structures on the biocompatible membranes permits, it may be possible to ensure the pores for cell migration/invasion are located at regions corresponding to the electrode surfaces, rather than in the gaps between electrodes or electrode elements[.]"

Claim 51 has been re-written in independent form and thus to recite all limitations in previous claims 50 and 24.

Claims 139-141 are amended to depend from claim 51.

Claim 143 has been re-written in independent form and thus to recite all limitations in previous claim 24.

Claim 157 is newly added, depends from claim 11 and adds, further comprising the step of introducing a known or suspected modulator of cell migration to the lower chamber of the device. Support may be found in paragraph [0024], which provides, "The method may also include introducing a known or suspected modulator of cell migration to the lower chamber of the device."

Claim 158 is newly added, depends from claim 11, and adds further comprising the step of introducing a known or suspected modulator of cell migration to the upper chamber of the device. Support may be found in paragraph [0025], which provides, "In another embodiment, the method includes introducing a known or suspected modulator of cell migration to the upper chamber of the device."

Claim 159 is newly added, depends from claim 11, and adds wherein the cells are mammalian cells. Claim 160 is newly added, depends from claim 159 and adds wherein the mammalian cells are cells known to be or suspected of being malignant. Claim 161 is newly added, depends from claim 159 and adds wherein the mammalian cells are neuronal cells. Support for claims 159-161 may be found in paragraph [0026], which provides, "The cells may be mammalian cells. In one embodiment, the mammalian cells are cells suspected of being malignant. In another embodiment, the mammalian cells are neuronal cells."

Claim 162 is newly added, depends from claim 51 and adds wherein the biocompatible membrane comprises one or more plastics or one or more polymers and further wherein the thickness of the membrane is from 5 microns to 50 microns. Support may be found in paragraph [00101], which provides in part,

> "The biocompatible membrane of the present apparatuses can comprise any suitable material. Non-limiting examples of the material include glass (e.g., quartz glass, lead glass or borosilicate glass), silicon, silicon dioxide on silicon, silicon-on-insulator (SOI) wafer, sapphire, plastics, and polymers.... Preferably, a biocompatible membrane of a device of the present invention is between about 5 and about 50 microns thick[.]"

Claim 163 is newly added, depends from claim 51 and adds wherein the biocompatible membrane comprises a coating that allows the attachment of one or more cells. Support may be found in paragraph [0021], which provides, "The biocompatible porous membrane may also include a coating for promoting the attachment of one or more cells thereto.

Claim 164 is newly added, depends from claim 163 and adds wherein the coating comprises an extracellular matrix component. Support may be found in paragraph [0080], which provides in part, "For example, a biomolecular coating can comprise an extracellular matrix component (e.g., fibronectin, collagens), or a derivative thereof[.]"

Claim 165 is newly added, depends from claim 51 and adds wherein for each of the plurality of isolated fluid containers that comprises a single IDES or CCES situated in a fluid container, the biocompatible membrane separates an upper chamber from a lower chamber of the fluid container. Support may be found in paragraph [00100], which recites in part, "the membrane separates the upper and lower chambers from one another[.]"

Claim 166 is newly added, depends from claim 165 and adds wherein said electrodes are fabricated on the lower side of said membrane, wherein said at least one pore has a diameter of between 1 micron and 30 micorns. Support may be found in paragraph [00155], which recites in part, "In other aspects of these embodiments, the electrodes are fabricated on the lower side of the membrane. In these aspects, the pores of the biocompatible membrane have a diameter of greater than about 1 micron, and preferably less than about 30 microns ...."

Claim 167 is newly added, depends from claim 166 and adds wherein said membrane comprises at least one biomolecular coating, at least one extracellular matrtix component, a layer of epithelial or endothelial cells, or a combination thereof, on the upper side of said membrane. Support may be found in paragraph [00155], which recites in part, "The upper side of the membrane can comprise at least one extracellular matrix component, and preferably comprises more than one extracellular matrix component that can form a matrix, such as, for example, Matrigel™.", and in paragraph [00156], which recites in part, "Alternatively or in addition, the upper side of the membrane can comprise a layer of epithelial or endothelial cells. "

Claim 168 is newly added, depends from claim 166 and adds wherein said device is used to assay the migration or invasiveness of one or more cells and wherein said lower chamber comprises at least one compound known to modulate the migration or invasiveness of cells, or at least one compound suspected of modulating the migration or

invasiveness of cells. Support may be found in paragraph [00158], which recites in part, "Such apparatuses can be used to assay the migration or invasiveness of one or more cells ..." and in paragraph [00156], which recites in part, "Optionally, one or more compounds that can affect the invasion/migration behavior of cells can be provided in the lower chambers of the apparatus." Support may also be found in paragraph [00181], which recites in part, "The buffer or medium loaded into the bottom chamber may comprise suitable reagents, *e.g.*, chemoattractants or other cell migration modulators that may stimulate or inhibit cell migration or reagents suspected of being cell migration/invasion modulators."

Claim 169 is newly added, depends from claim 166 and adds wherein said device is used to assay the migration or invasiveness of one or more cells and wherein said upper chamber comprises at least one compound known to modulate the migration or invasiveness of cells, or at least one compound suspected of modulating the migration or invasiveness of cells. Support may be found in paragraph [00158], which recites in part, "Such apparatuses can be used to assay the migration or invasiveness of one or more cells ..." and in paragraph [00156], which recites in part, "Optionally, one or more compounds that can affect the invasion/migration behavior of cells can be provided in the upper chambers of the apparatus." Support may also be found in paragraph [00181], which recites in part, "Appropriate reagents (e.g. cell migration/invasion modulators that stimulate or inhibit cell migration/invasion or reagents suspected to be cell migration/invasion modulators) may be added into the top chamber..."

Response to Allowable Subject Matter

Claims 11, 51 and 142-156 were objected to as being dependent from a rejected base claim. Thus, the examiner indicated the claims would be allowable if re-written in independent form including all of the limitations of the base claim and any intervening claims.

Applicants have re-written claims 11, 51 and 143 in independent form including all the limitations of the base claim and any intervening claims. Claim 142 depends from claim 51 and claims 144-156 depend from claim 143.

Further, Applicants have amended claims 139-141 to depend from claim 51; provide new claims 157-161, which depend from claim 11; and provide new claims 162-169, which depend from claim 51.

Applicants respectfully request claims 11, 51 and 142-156 be allowed as well as amended claims 139-141 and new claims 157-169.

Response to Claim Rejections - 35 USC § 102

I.
Claims 1, 6, 9, 10, 24, 43, 50, 62, 65, 68, 69 and 139 are not anticipated by Sparks under 35 USC § 102(e)

The examiner has rejected claims 1, 6, 9, 10, 24, 43, 50, 62, 65, 68, 69 and 139 under 35 USC § 102(e) as allegedly being anticipated by Sparks (US 6,637,257). With respect to claim 1, the examiner argues Sparks discloses a device that is structurally capable of monitoring cell migration or invasion of a biological particle including an upper chamber **30**; a lower chamber **30** comprising at least two electrodes **20, 22**; and a biocompatible porous membrane **12** having a porosity **14** sufficient to allow cells to migrate therethrough, wherein the membrane is disposed in the devices so as to separate the upper and lower chambers from one another, wherein the at least two electrodes are disposed on the membrane; wherein the cell can contact one or more of the electrodes; wherein the electrodes have substantially the same surface area (**FIG. 2**) and further wherein contact of a cell with the electrodes provides a detectable change in impedance between or among the electrodes (Col. 4, ll. 14-31). The Examiner notes that while the upper chamber in **FIGS. 3** and **4** includes the electrodes the device is structurally the same as the instantly claimed regardless of the orientation of the device.

A. The device of claim 1 is structurally different than Sparks because the porous membrane of Applicant's invention is sized to allow cells to migrate therethrough and detection occurs in the lower chamber; whereas the vias in Sparks are sized to prevent cells to pass therethrough and detection occurs at the first surface (which would correspond to Applicants upper chamber) and such limitations are intended as a structural requirement in Sparks

Claim 1 provides a biocomapatible porous membrane having a porosity sufficient to allow cells to migrate therethrough. For clarity, Applicants further provide migration occurs from the upper chamber to lower chamber. Thus in Applicants' claim 1 the structure of the porous membrane is specifically adapted for the passage of cells and the detection specifically occurs at the membrane in the lower chamber. In other words, Applicants' configuration detects cells that exit the pore and attach on the bottom side of the membrane.

In contrast, the vias in Sparks are specifically intended and thus structurally designed to prevent passage of cells when a fluid containing the cells or particles is flowed through the vias. Detection occurs spatially before entry of the via. Referring to Col. 2, lines 44-50,

> "First and second electrodes are, located on the first surface of the substrate so that the materials too large to pass through the vias, and have therefore collected at the first surface of the substrate, will electrically connect the first and second electrodes to produce an output signal in proportion to the amount of the material collected."

Now referring to Col. 3, line 66 to Col. 4, l. 13,

> "In view of the above, the diameter of the vias **14** is chosen to prevent the passage through the substrate **12** of cells/ particles of a particular size and larger, while permitting the entraining fluid and smaller cells/particles **25** to pass through the substrate **12**. For example, leukocytes (diameter of about twenty micrometers) can be filtered with an array of vias **14** on the order of about fifteen to seventeen micrometers in diameters, while allowing water (95% of urine), electrolytes, protein, glucose, and erythrocytes to pass through. The monitoring of the presence of erythrocytes in urine is also desirable as being useful to detect cardiovascular, renal, and hepatic problems. For this purpose, erythrocytes (about eight micrometers in diameter) can be subsequently filtered with a second substrate **12**

having appropriately-sized vias **14**, e.g., having a size range of about three to seven micrometers." (emphasis added)

Since the device in Sparks is specifically designed to prevent the passage of cells, the elements and configurations in Sparks must be interpreted with respect to these recited functional limitations. In other words, there are specific structural limitations or configurations that must be included when applying Sparks. Specifically, Sparks indicates the "diameter of the vias **14** is chosen to prevent the passage through the substrate **12** of cells/particles of a particular size and larger." Thus the sizing of the vias includes corresponding structural limitations, being smaller than the cells to be excluded.

While the Examiner in essence indicates the purpose of using the device provided in Sparks gives no patentable weight, Sparks specifically incorporates the purpose into the design requirements or design tolerances and thus in this instance provides structural limitations to claim. Specifically the device in Sparks is a filter that prevents the passage of cells, and the electrodes detect the build up of filtered cells or those cells that can not pass through the vias. Referring to Col. 2, ll. 20-26,

> "The present invention provides a method and device for performing fluid analysis utilizing a micromachined filter to separate cells and/or particles from a fluid, such as a biological fluid. The device has the additional capability of sensing the relative quantity of cells and/or particulate material selectively separated from the fluid with the filter."

Thus while the intended use of Sparks is to separate cells by preventing their passage, Sparks provides specific structural limitations that must be considered when applying the disclosure. In other words, the elements of Sparks must be read with respect to these structural limitations. Specifically, the electrodes in Sparks are positioned on the surface that prevents passage of cells and not on the surface or side where cells exit the vias. Therefore the orientation of the Sparks device is a specific limitation that must be applied.

In contrast, Applicants' device in claim 1 includes a structural limitation that allows the migration of cells. Specifically, Applicants provide a biocomapatible porous membrane having a porosity sufficient to allow cells to migrate therethrough. Moreover detection occurs in the lower chamber or the chamber into which the cells migrate.

Applicants respectfully request the rejection be withdrawn.

B. Applicants' claim 1 recites the migration of cells through the porous membrane permits attachment of cells that have migrated to the lower chamber on one or more of at least two electrodes of the lower chamber; whereas in Sparks cells are collected due to the inability to traverse the vias and the collected cells do not attach to electrodes

In Applicants' claim 1 the migration of cells through the porous membrane permits attachment of cells that have migrated to the lower chamber on one or more of at least two electrodes of the lower chamber. In other words, in Applicants' invention the cells can attach to the electrodes after migration.

In contrast, the filtration system in Sparks does not facilitate attachment of cells that traverse a porous membrane but instead detects cells that block the vias. In other words in Sparks, contact between electrodes and cells occurs by physical blockage due to collection and does not occur by attachment. Referring to Col. 2, ll. 44-50,

> "First and second electrodes are, located on the first surface of the substrate so that the materials too large to pass through the vias, and have therefore collected at the first surface of the substrate, will electrically connect the first and second electrodes to produce an output signal in proportion to the amount of the material collected." (emphasis added)

Since Sparks does not demonstrate each and every element of claim 1, Applicants respectfully request the rejection be withdrawn.

C. Applicants' claim 1 recites the at least two electrodes are partially exposed through pores of the porous membrane whereas in Sparks the electrodes are not exposed through the via

Applicants have amended claim 1 to recite the at least two electrodes are partially exposed through pores of the porous membrane. By providing such exposure, once cells migrate through the pores, they come into contact with and can attach to the electrode surface.

Referring to Sparks, the electrodes are not exposed through the vias but instead are positioned entirely on the solid portion of the substrate. This configuration permits the device in Sparks to be used a filtration device. Referring to Col. 3, ll. 41-44,

> "As seen in FIG. 2 the vias **14** are arranged in an array (rows and columns), with rows of the vias **14** being separated by interdigitated portions of two electrodes **20** and **22** on the upstream surface of the substrate **12**."

Viewing FIGS. 1 and 2 it is clear the electrodes are entirely on the solid portion of the substrate and are not exposed through vias. This configuration is consistent with a device that detects cells that do not pass through the vias. Since Sparks does not teach each and every element of Applicants' invention, Applicants respectfully request the rejection be withdrawn.

D. Sparks does not anticipate claim 24

Claim 24 has been amended to recite the at least two electrodes are partially exposed through pores of said porous membrane. As discussed above, in Sparks the electrodes are positioned entirely along the solid portion of the substrate and are not exposed through vias. In addition, Applicants incorporate by reference the description that Sparks requires detection prior to entry of the via.

Applicants respectfully request the rejection be withdrawn.

E. Claims 6, 9, 10, depend from claim 1 and claims 43, 50, 62, 65, 68 and 69 depend from Claim 24

The above arguments with respect to claim 1 and 24 are incorporated herein by reference. Claims 6, 9, 10, depend from claim 1 and claims 43, 50, 62, 65, 68 and 69 depend from claim 24. Thus since Sparks is deficient with respect to claims 1 and 24, Applicants respectfully request claims 6, 9, 10, 43, 50, 62, 65, 68 and 69 also be allowed.

F. Claim 139 newly depends from claim 51

Applicant has amended claim 139 to depend from claim 51. Since claim 51 depends from an allowable claim, now provided in independent form, Applicants respectfully request claim 139 be allowed.

Response to Claim Rejections – 35 USC § 103

I.

Claims 140 and 141 are not obvious over Sparks (US 6,637,257)

The Examiner has rejected claims 140 and 141 as allegedly being obvious over Sparks. Applicants have amended claims 140 and 141 to depend from claim 51. Claim 51 has been re-written in independent form and was previously deemed allowable subject matter. Thus Applicants respectfully request the rejection be withdrawn.

II.

Claims 8, 24, 25, 28, 29, 43, 50, 62, 65, 68, 69 and 139 are not obvious over Sparks (US 6,637,257 in view of Shah (US 5,247,827)

The Examiner has rejected claims 8, 24, 25, 28, 29, 43, 50, 62, 65, 68, 69 and 139 as allegedly being obvious over Sparks in view of Shah. Applicant incorporates by reference the above description of Sparks.

With respect to claim 1, from which claim 8 depends, Sparks does not provide: a) a porous membrane sufficient to allow cells to migrate therethrough from the upper chamber to the lower chamber; b) at least two electrodes disposed on the membrane and partially exposed through pores of the porous membrane; or c) migration of cells through the porous membrane permits attachment of cells that have migrated to the lower chamber on one or more of the at least two electrodes.

Shah provides a device for detecting the conductivity of particulate matter, such as dust, carried in air or other gasses. Referring to Col. 1, line 61 to col. 2, line 2,

> "Air is pumped through a filter having a mesh size sufficiently small to filter out the particles. An interdigitated electrode structure is formed on the upstream side of the filter. The conductivity of the dust is determined by measuring the electrical resistance between the electrodes."

With respect to claim 8, Shah does not provide the deficiencies from claim 1, from which claim 8 depends. Specifically Shah filters dust from air or gas and does not permit cells to migrate through the filter. Similarly Shah detects dust upstream whereas in Applicants' invention detection of cells occurs in the lower chamber or downstream in comparison to Shah. Though Shah appears to place electrodes on a filter it does not indicate whether the electrodes are exposed through a pore; however placement along a solid portion would be consistent with the filtration device as provided by Sparks.

With respect to claim 24, neither Sparks nor Shah provide a surface suitable for cell attachment or cell growth. In addition, being consistent with the filtration device as provided by Sparks, the electrodes are placed on the solid portion of the substrate and are not exposed through a pore. Yet, in claim 24, the electrodes are partially exposed through pores of the porous membrane.

Claims 25, 28, 29, 43, 50, 62, 65, 68, and 69 depend from claim 24. Since neither Sparks nor Shah provide the deficiencies of claim 24, claims 28, 29, 43, 50, 62, 65, 68, and 69 are not obvious over Sparks in view of Shah.

With respect to claim 139, claim 139 has been amended to depend from claim 51. Claim 51 was deemed to include allowable subject matter and has been re-written in independent form.

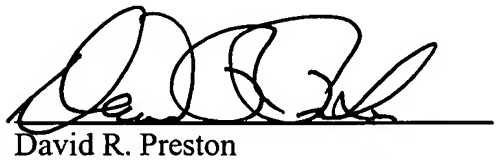
Applicants respectfully request the Examiner withdrawal the above rejections and provide a notice of allowance for the present application.

Conclusion

In view of the amendments and argument set forth above, Applicants respectfully request all rejections be withdrawn and a notice of allowance be issued in this case.

Respectfully submitted,

Date: May 27, 2008



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